A monograph and self-assessment examination for CME credit

On The Cover

Above: Electron micrograph of hepatitis A virus particles in vitro.

Below: Jaundice is a symptom commonly associated with hepatitis A. However, among children under 6 years of age, 70% of infections are asymptomatic and symptomatic cases in children usually do not have jaundice.

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Intended Audience

Family physicians, physician assistants and nurse practitioners

Objectives

Upon completion of this activity, paricipants should be able to:

- Define risk factors for Hepatitis A
- Describe symptomology for Hepatitis A
- Discuss treatment for Hepatitis A

Accreditation

Course No. 483MED

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Washington School of Medicine and the University of Washington School of Public Health and Community Medicine. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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Within three weeks following the receipt of this form, a transcript of your category 1 hours will be mailed to you. Credit hours for this monograph may be obtained from April 2001 through April 2004.

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Introduction

Hepatitis A is the most frequently reported vaccinepreventable disease in the United States and is the most common form of acute viral hepatitis in much of the world. Although mortality associated with acute hepatitis A is infrequent, acute liver failure due to severe hepatitis A results in approximately 100 deaths each year in the United States. The case-fatality rate for fulminant hepatitis A among persons of all ages with acute hepatitis A reported to the Centers for **Disease Control and Prevention** (CDC) is approximately 0.3% but is 1.8% among adults greater than 50 years of age. Persons with chronic liver disease, including that associated with chronic hepatitis C virus infection, are also at

increased risk for fulminant hepatitis A.

√ Hepatitis A is a common vaccine-preventable disease.

√ Serious complications are rare. The highest case-fatality rates occur in children less than 5 years old, adults greater than 50 years old and persons with underlying chronic liver disease.

Available studies on the economic impact of hepatitis A suggest the costs are substantial. Between 11% and 22% of persons with hepatitis A are hospitalized, and adults who become ill lose an average of 27 days of work. Average (indirect and direct) costs per case of hepatitis A have been reported

to range between \$1,817 to \$2,459 per case for adults and \$433 to \$1,492 for children less than 18 years of age. Outbreaks of hepatitis A also are costly—a common source foodborne outbreak in Denver. Colorado in 1992 involving 43 persons and approximately 5000 potential exposures was reported to cost over \$800,000. The CDC estimated annual costs of hepatitis A in the United States for the year 1989 to be more than \$200 million, equivalent to more than \$300 million in 1997 dollars.

 ▼ The economic impact of hepatitis A is considerable: an average adult case costs several thousand dollars and frequently results in several weeks of lost employment.

Clinical Features

Hepatitis A virus (HAV) is a 27-nm RNA virus in the Heparnavirus genus of the picornavirus family (which also contains viruses in the Enterovirus genus) (*Figure 1*). The disease is spread from person to person with no known zoonotic reservoir.

HAV may produce symptomatic or asymptomatic infection of the liver after an average incubation period of 28 days (range 15-50 days). Clinical illness occurs in most older children and adults, and is characterized by abrupt onset of constitutional and gastrointestinal symptoms (Table 1). Prodromal symptoms include variable combinations of fever, chills, malaise, anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgias, and myalgias. Cigarette smokers with hepatitis A classically report a decreased desire for tobacco. In 70% of older children and adults, prodromal symptoms are followed in 1-7 days by onset of dark urine, clay-colored stools, and jaundice. Pruritis secondary to cholestasis may occur. Physical findings can include icterus, an enlarged and sometimes tender liver, and less commonly an enlarged spleen. Atypical symptoms are more commonly seen in children and include flulike symptoms of pharyngitis,

cough, coryza, arthralgias, photophobia, and headache. The duration of illness is variable although most persons are markedly improved by the third week. The course of hepatitis A appears unchanged in pregnancy and adverse consequences to fetal health or survival are not known to occur.

√ After an average incubation period of 28 days, infected adults have nonspecific constitutional and gastrointestinal symptoms, followed by onset of dark urine, clay-colored stools, and jaundice.

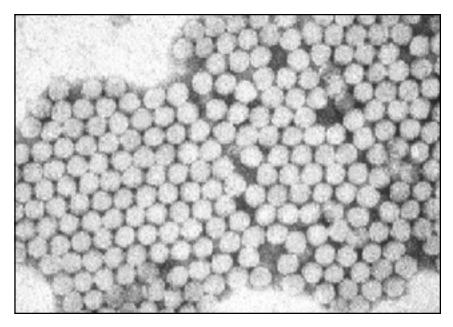
Among children under 6 years of age, 70% of infections are asymptomatic and symptomatic cases usually do not have

jaundice. Although clinical illness usually lasts up to 2 months, approximately 10-15% of individuals may have prolonged or relapsing disease for up to 6 months. The prognosis for complete recovery in relapsing disease is excellent despite the prolonged course.

√ Children <6 years of age with hepatitis A usually have asymptomatic infections or atypical manifestations.

Complications of hepatitis A include cholestasis, prolonged and relapsing disease, fulminant hepatitis, and triggering of chronic active autoimmune hepatitis or autoimmune extrahepatic disease. Rare complications of acute hepatitis A include cutaneous necrotizing

Figure 1. Electron micrograph of hepatitis A virus particles



vasculitis and mononeuritis multiplex.

Acute liver failure is characterized by worsening liver chemistry and function with rising transaminases (ALT, AST) and bilirubin, and coagulopathy with prolonged prothrombin time (PT) and change in mental state. Early signs may include lethargy, irritability, insomnia, confusion, and severe vomiting. Cerebral edema and multiple organ failure lead to death in 70-95% of cases. The most important feature of clinical management is early referral for liver transplantation, which may result in survival rates of 65% or greater. There is substantial evidence that the disease is more likely to be fulminant in persons with underlying liver disease, particularly cirrhosis.

√ Cases progressing to acute liver failure require early referral for liver transplantation.

HAV replicates in the liver, is excreted in bile, and is shed in the stool. Viremia occurs soon after infection and persists through the period of liver enzyme elevation. The peak of infectivity with highest concentration of virus in the stool is during the 2-week period before

symptom onset or elevation of liver enzymes. Infectivity and the concentration of virus in stool decline rapidly during the week following the onset of jaundice. Children and infants can shed the virus longer than adults, up to months after the onset of clinical illness. There is no chronic intestinal carrier state for hepatitis A, however relapsing disease may occur (particularly in children) with intermittent shedding of virus.

√ Persons are most infectious before they feel ill, with peak infectivity a full two weeks before any symptoms develop.

Table 1. Clinical features of hepatitis A infection in adults*

Signs & symptoms:

- Fever
- Chills
- Malaise
- Anorexia
- Weight loss
- Vomiting
- Nausea
- Abdominal discomfort
- Diarrhea
- Arthralgia
- Dark urine (>75%)
- Jaundice (>75%)

Clinical findings:

- Slightly tender hepatomegaly (usually)
- Posterior cervical lymphadenopathy (occasionally)
- Splenomegaly (rarely)

Laboratory findings:

- Elevated ALT/AST (SGPT/SGOT)
- 500-5000 U/L at peak infectivity; transaminases may be as low as 200 U/L in acute infection
- Elevated serum bilirubin (rarely above 1.70 mg/dl)
- Anti-HAV IgM (diagnostic of acute infection)

*In children <6 years old, 70% are asymptomatic. When children are symptomatic, they usually lack typical adult findings such as jaundice. More commonly, children present with flu-like symptoms such as pharyngitis, cough, coryza, arthralgia, photophobia, and headache.

Diagnosis

Hepatitis A cannot be differentiated from other viral hepatitis on clinical and epidemiologic features alone. Liver function tests, especially serum ALT and AST, are sensitive but nonspecific indicators of hepatic parenchymal damage. Serum aminotransferase levels are typically in the 1000-2000 U/L range (normal approximately 35 U/L) and ALT levels return to normal by a mean of 7.4 weeks. Alkaline phosphatase levels are usually only mildly elevated; persisting elevated levels suggest associated cholestasis.

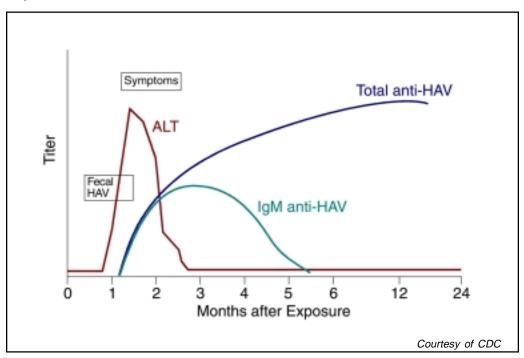
√ Liver function tests demonstrate elevated aminotransferases (ALT and AST) with milder elevations in alkaline phosphatase.

The diagnosis of acute hepatitis A is confirmed by detection of specific immune globulin M (IgM) anti-HAV in serum by commercially available assays (*Figure 2*). IgM can be detected 5-10 days before the onset of symptoms and typically for 3-6 months after infection (25% of cases have detectable levels for up to 12 months). To diagnose or rule-out acute hepatitis A infection, it is important to

order an IgM anti-HAV. Immunization can induce temporary detectable levels of IgM anti-HAV in a minority of persons. Assays for total antibody to HAV are not useful because immune globulin G (IgG) may be detectable for many years after past infection and confers lifelong immunity. HAV RNA amplification and nucleic acid sequencing for relatedness of isolates can be done in a research laboratory setting.

√ Laboratory detection of anti-HAV IgM is necessary for the diagnosis of acute hepatitis A.

Figure 2. Clinical symptoms, viral shedding (fecal HAV), transaminase levels (ALT), and serologic responses (anti-HAV) after hepatitis A infection



Epidemiology

General overview

The epidemiology of hepatitis A is strikingly heterogeneous. From year to year and community to community, the at-risk populations with the highest rates of hepatitis A can shift. In King County during 1998, 40% of hepatitis A cases were among men who have sex with men (MSM), while in 1999 this figure dropped to 8%. In a given community during a given time period the predominant risk group for hepatitis A infection may be illicit or injecting drug users (IDU), MSM, child daycare center attendees and their contacts, or the general population with no recognized risk factors. This emphasizes the importance of identifying and immunizing all persons with indications for hepatitis A vaccine in the community if long-term control of hepatitis A transmission is to be achieved.

√ Rates of hepatitis A and groups at risk for infection may vary considerably from year to year and between communities.

The U.S. national incidence averages 10 cases per 100,000 persons but rates vary significantly by region with substantially higher rates in the western United States, including Washington State. During 1987-1997, an average of 50% of reported hepatitis A cases each year in the United States were from 11 mostly western states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, California) yet the total population of these states represented approximately 22% of the U.S. population (see *Hepatitis A in Washington State*, on page 11).

√ The western United States, including Washington State, have substantially higher rates of hepatitis A.

Incidence rates of hepatitis A can remain fairly constant, or undergo cyclical or sporadic peaks with periodic outbreaks. In the United States, cyclic increases in the incidence of hepatitis A have occurred approximately every decade with peaks in 1953, 1961, 1971, and 1989. The last statewide epidemic in Washington occurred in 1986-1990, when infection rates peaked at 70 cases per 100,000 persons, approximately 5 times the national average. No seasonal variation has been seen with hepatitis A epidemics.

Epidemiologic patterns in communities

Many hepatitis A cases in the United States occur in the context of community-wide epidemics. Using incidence data, CDC stratified communities into low, intermediate, and high risk of hepatitis A. Highrisk communities typically have epidemics every 5-10 years that can last for several years, with peak incidence during epidemics greater than 700 cases per 100,000 persons. Most adults have protective antibodies from past exposure, and new cases are primarily in children less than 15 years old. These communities are often well defined either geographically or culturally, may have crowding or low economic status, and include certain American Indian. Alaskan Native, Hispanic, migrant and religious communities. Reductions in disease incidence and prevention of outbreaks in these communities have been achieved with routine, sustained immunization of young children.

√ High- and intermediaterisk communities can reduce disease incidence by routine, sustained immunization of young children.

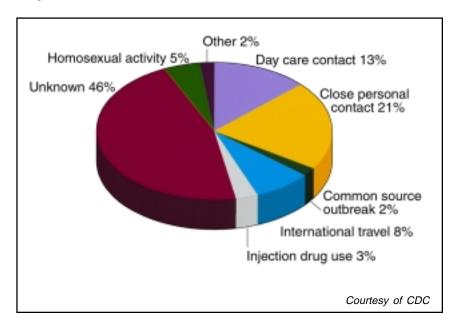
Intermediate-risk communities can have periodic epidemics affecting a wider range of ages or simply sustained elevated rates without cyclic changes. Metropolitan areas are frequently in this category. Overall incidence rates during epidemic periods range from 50-200 cases per 100,000 persons. During epidemic periods, hepatitis A rates increase among all age groups indicating widespread disease in the community but often concentrate in certain risk groups or geographic areas. In communities with sustained elevated rates, children with asymptomatic hepatitis A infection can be a substantial source of infection for older persons. Because of barriers in accessing and maintaining vaccine coverage in at-risk individuals, targeted immunization programs have not been a satisfactory public health strategy to control outbreaks in intermediate-risk communities.

Low-risk communities report most cases among school-age children, adolescents, and young adults. Little year-to-year variation is reported, and community outbreaks are uncommon.

Sources of infection

Several major risk factors are consistently reported in association with hepatitis A cases (*Figure 3*). Most U.S. cases of hepatitis A result from personto-person transmission during community-wide outbreaks. The most frequently reported source of infection (12-26%) is either

Figure 3. Risk factors associated with reported hepatitis A cases in the U.S., 1997



household or sexual contact with an infected person. Approximately 11-16% of reported cases occur among children or employees in day-care centers or among their contacts. Asymptomatic infection of children serves as an important reservoir through which the virus maintains its endemicity.

√ Since infected children are frequently asymptomatic, they are an important and frequently unrecognized source of infection.

√ Other important risk factors include men who have sex with men, illicit drug use, and international travel.

International travelers account for 8% of cases nationally with Mexico, Central and South America accounting for 84% of travel-related infections. Approximately a third of travelrelated infections occur in children. Although 2-3% of all cases are associated with recognized food- or waterborne disease outbreaks, the actual burden of disease related to foodborne transmission is not known.

Cyclical epidemics of hepatitis A among men who have sex with men (MSM) and injecting drug users (IDU) can be particularly significant in urban areas. During outbreak years, up to 10% of cases nationally and the majority of cases in specific communities may occur among persons reporting these behaviors.

Despite the above well-described risk factors for hepatitis A, approximately half of all reported cases have no recognized risk factors. Thus, targeted hepatitis A immunization

programs that concentrate only on specific high-risk groups have had little sustained impact on community-wide rates of hepatitis A. Based on CDC sentinel county data, a third of such cases involved a household with a child less than 5 years of age in the house. Again this suggests that asymptomatic cases among children serve as an important mechanism of disease spread.

√ Half of all hepatitis A cases have no recognized risk factor.

Transmission

Hepatitis A is transmitted directly or indirectly by the fecal-oral route, either by person-to-person contact or ingestion of contaminated food or water. Close contact in settings with less than optimal hygiene facilitates the transfer of the virus. Infected persons are most likely to transmit HAV 1-2 weeks before the onset of illness. Infectivity usually decreases markedly during the week after the onset of jaundice but prolonged viral excretion in stools has been documented in infants, children, and persons with HIV infection. Secondary attack rates of clinically apparent infections among household members approach 20-50%. Although the virus can be detected in saliva, urine, and semen, infectivity of these fluids has not been documented and is speculative.

Hepatitis A can rarely be transmitted through transfusion of blood or blood products collected from donors during the viremic phase of infection.

Vertical transmission has not been reported as a mechanism of infection.

√ Hepatitis A is transmitted by the fecal-oral route. Secondary attack rates of clinically apparent infections among household members approach 20-50%.

Common-source foodborne outbreaks typically result from contamination by an HAV-infected food handler during the disease incubation period. Such foods as salads, sandwiches, iced or glazed pastries, and dairy products have been reported in food-related outbreaks. Rarely foods that are gathered and then served raw, such as strawberries, lettuce, and raspberries, are

attributed to an outbreak; a multistate outbreak in 1997 was traced to frozen strawberry production in Mexico. Ingestion of uncooked or undercooked shellfish (clams, oysters, and mussels) has led to hepatitis A infection when the shellfish came from contaminated areas.

√ Infected food handlers have been responsible for outbreaks of hepatitis A.

Specific high-risk populations and persons at risk for serious outcomes

Travelers

Hepatitis A is the most common vaccine-preventable infection of travelers to developing regions of the world (*Figure 4*). The incidence of infection is estimated to be 3-5 cases per 1000 persons per month of stay. Measures taken to prevent infection—such as luxury hotel

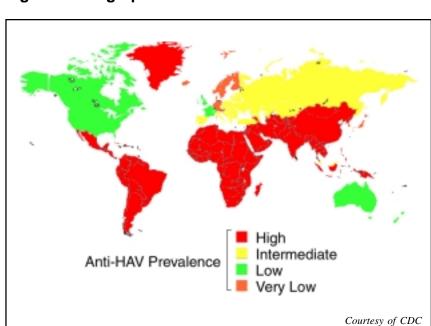


Figure 4. Geographic distribution of HAV infection

accommodations in urban areas, vigilant food and water selection, and good hygiene—are generally ineffective. Rates are influenced by local sanitary and hygienic standards, duration of travel, deviation from usual tourist routes, and the reservoir of infection in the local population. Groups at particularly high risk include missionaries, Peace Corps volunteers, and U.S. Foreign Service members in developing countries.

Fecal contamination of water may be the leading source of hepatitis A infection in developing countries. Drinking water, consuming ice, or swimming in polluted ocean or fresh water can place a traveler at increased risk of infection. The virus is relatively stable in the environment and requires boiling for greater than 3 minutes to be inactivated. Various factors contribute to hepatitis A infection in travelers (*Table 2*).

Men who have sex with men Although outbreaks of hepatitis A have been reported frequently among men who have sex with men (MSM), overall rates in this group are not significantly elevated. However, prolonged, cyclical urban outbreaks of hepatitis A with sustained transmission over several years have been associated with male homosexual behavior. Among MSM, oral-anal contact, digital rectal intercourse, the number of sexual partners and history of multiple sexually transmitted

Table 2. Factors contributing to hepatitis A infection in travelers

- Boiling water for less than 3 minutes
- Using hand-held pump filters (hepatitis A not removed)
- Using insufficient concentration of or contact time with chlorine or iodine for water purification
- Using hot water to brush teeth
- · Consuming ice or drinks made with unpurified water
- Steaming shellfish (hepatitis A not inactivated)
- Eating salads and unpeeled fruits

From Wolfe, MS. (1995)

diseases are associated with an increased likelihood of contracting hepatitis A.

Injecting and noninjecting illicit drug users

Both injecting and noninjecting illicit drug users are at risk for hepatitis A. Recently, increased rates of hepatitis A have been associated with methamphetamine (crank) use. Hepatitis A infection among drug users results primarily from behaviors associated with lower socioeconomic status, such as crowding and poor hygiene. Percutaneous transmission probably occurs to a much less extent.

Persons with clotting-factor disorders
Several reports have linked hepatitis A infection in persons with hemophilia and other clotting-factor disorders to transfusions with clotting-factor concentrates that did not undergo the currently preferred method of virus inactivation

(pasteurization, vapor heating, or psoralen/ultraviolet A treatment). Persons receiving therapy with blood products manufactured using currently preferred methods of virus inactivation in the United States are not at risk for hepatitis A.

Persons working with non-human primates
Outbreaks have been reported among individuals working with several Old World and New
World primates that are susceptible to hepatitis A infection and born in the wild. This is the only occupationally related risk factor for hepatitis A infection currently recognized by CDC.

Persons with chronic liver disease
Although not at increased risk for hepatitis A infection, persons with chronic liver disease who contract hepatitis A are at increased risk of fulminant hepatitis and death.

Surveillance of Hepatitis A

Health-care providers are required by law in Washington State to report suspected or confirmed cases of hepatitis A immediately to their local health department. Laboratories are also required to report all IgM anti-HAV positive results within 48 hours. Such reporting is necessary to allow prompt disease investigation, outbreak recognition, and control activities. Specifically, the goals of surveillance as stated by the CDC are to: (1) provide postexposure prophylaxis for contacts of cases, (2) detect outbreaks, (3) determine the effectiveness of hepatitis A immunization, (4) monitor incidence of symptomatic disease, (5) determine the epidemiologic characteristics of infected persons, including outbreak sources, and (6) determine missed opportunities for immunization.

√ Health-care providers in Washington are required to report suspected or confirmed cases of hepatitis A immediately to their local health department.

Hepatitis A has been under surveillance as a reportable disease since 1952. There is underreporting of symptomatic cases and virtually no reporting of asymptomatic cases. Given this, it can be difficult to generate reliable risk data.

Hepatitis A in Washington State

Incidence rates of hepatitis A have been consistently higher in Washington State than in the United States (*Figure 5*). From

1994 to 1998, the rate of hepatitis A in Washington State was 18.5 cases per 100,000 persons, compared with the U.S. average of 10 cases per 100,000. The rate in 13 of

Figure 5. Incidence of hepatitis A in Washington State and the US, 1966-1998

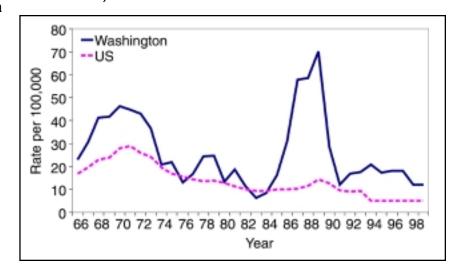
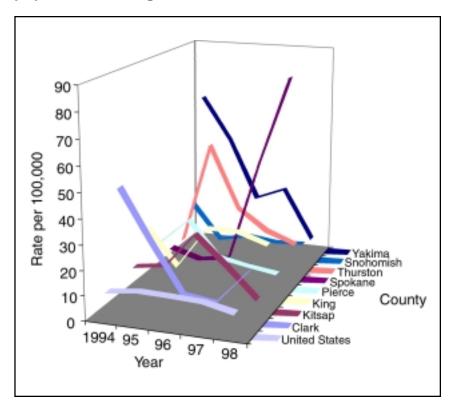


Figure 6. Incidence of hepatitis A in the 8 most populous Washington counties and the US, 1994-1998



Washington's 39 counties exceeded 20 cases per 100,000 persons. These 13 counties accounted for 73% of the cases reported during that time period. While year-to-year rates within counties may vary considerably, many counties consistently have rates greater than the national average without including the epidemic period 1986-1990 (*Figure 6*).

√ Hepatitis A rates in Washington State are nearly twice the national average.

Men are more likely than women to acquire hepatitis A by a factor of 1.5:1. This is due to a male predominance among high-risk groups. Hepatitis A was more often reported among young adults in the 20-39 year old age range (Figure 7). Among ethnic groups, Native Americans have the highest incidence of hepatitis A (*Figure 8*). Injection drug use was the most frequently identified risk factor in Washington when a risk factor other than case contact was reported (Figure 9).

Figure 7. Reported cases of hepatitis A in Washington by age group, 1990-1999

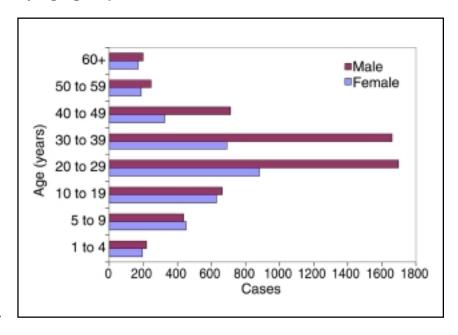


Figure 8. Incidence of hepatitis A in Washington by race, 1998

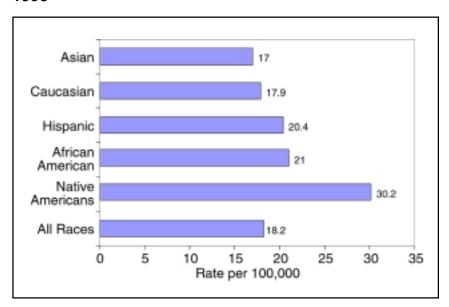
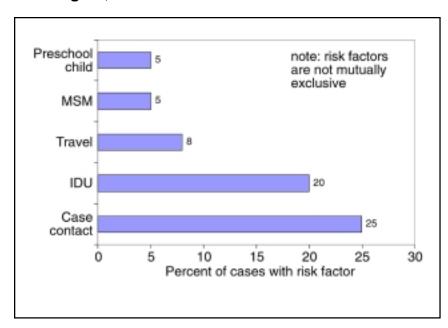


Figure 9. Risk factors reported for cases of hepatitis A in Washington, 1994-1999



Treatment

There is currently no specific therapy available for hepatitis A and complete recovery occurs in almost all cases. Management of acute symptomatic disease is supportive, with hospitalization reserved for complicated cases. The most important management issue is prompt recognition of fulminant hepatitis and referral for evaluation for liver transplantation. It is also recommended that patients with hepatitis A abstain from alcohol consumption.

- √ No effective treatment exists for acute hepatitis A.
- √ The most important management fissue is prompt recognition of fulminant hepatitis and referral for evaluation for liver transplantation.

Prevention

Persons with hepatitis A as well as other enteric infections can minimize transmission of infection by thorough hand washing, especially before preparing food. All food handlers need to be especially careful regarding measures to prevent transmission of infectious agents. It is important that food handlers not work while ill with enteric diseases. In developing countries, the most important means of prevention of hepatitis A is through improvements in standards of hygiene and sanitation.

- √ Careful hand washing can minimize transmission of enteric organisms.
- √ Food handlers ill with enteric infections should not work.

Passive Immunization with Immune Globulin (IG)

IG is a sterile preparation of concentrated antibodies made from pooled human plasma processed by cold ethanol fractionation. In the United States only plasma that has tested negative for hepatitis B surface antigen, antibodies to human immunodeficiency virus (HIV) and antibodies to hepatitis C virus (HCV) is used to produce IG. A viral inactivation step or testing of the final product for hepatitis C by polymerase chain reaction (PCR) is also required. No transmission of hepatitis B, HIV, HCV, or other viruses has been reported from intramuscular administration of IG.

Passive immunization with intramuscular IG can prevent or lessen the course of hepatitis A infection through passive transfer of antibody, if given within 2 weeks after exposure. Before the availability of hepatitis A vaccine, IG administration was the standard means of hepatitis A prevention among travelers. However, benefit is temporary and dosedependent, with maximum doses achieving protection for 4-6 months. The CDC has issued guidelines for use of IG in outbreak settings (Table 3), although passive immunization has not been effective in stopping large-scale epidemics. IG can interfere with the response to live, attenuated vaccines other than oral polio vaccine.

Do not give MMR for at least 3 months or varicella vaccine for at least 5 months following administration of IG for hepatitis A prophylaxis. IG should not be administered within 2 weeks after the administration of MMR or within 3 weeks after varicella vaccine unless the benefits of IG administration outweigh the benefits of immunization. Thimerosal-free preparations of IG are considered safe for use during pregnancy and breast-feeding. IG should not be administered to persons with IgA deficiency.

√ Persons who have been exposed to hepatitis A and are susceptible should be administered IG intramuscularly (0.02 ml/kg) within 2 weeks of their last exposure.

Persons who have been exposed to hepatitis A and are susceptible should be administered a dose of 0.02 ml/kg IG intramuscularly within 2 weeks of their last exposure. Persons who have had one dose of hepatitis A vaccine at least one month before exposure to HAV do not need IG. Serologic confirmation of acute HAV in index patients by IgM anti-HAV testing is recommended before administration of IG to contacts. If hepatitis A vaccine is also recommended for a person being given IG; it may be administered simultaneously at a separate injection site. The use of hepatitis A vaccine alone is not recommended for postexposure prophylaxis.

Table 3. Indications for passive immunization with immune globulin in outbreak settings

Setting

Household, sexual contacts, and persons who have shared illicit drugs with serologically confirmed cases of hepatitis A.

All unvaccinated attendees or employees at a day-care center if: (1) at least 1 case of hepatitis A is an attendee or employee, or (2) hepatitis A cases present in 2 or more households of those who attend.

Comments

Consideration for others with ongoing contact (e.g. regular babysitter).

In day-care centers that do not take care of children in diapers, immune globulin is needed in classroom contacts only. When an outbreak occurs (3 or more families), IG should be considered for members of households that have children (center attendees) in diapers.

In common source outbreaks involving food handlers, immune globulin is recommended for:

- (1) other food handlers at the same establishment, and
- (2) patrons only if that person is contacted within 2 weeks after suspected exposure, and if the particular index case is known to have had poor hygiene and handled food after cooking.

In school, hospitals, and work settings, with an outside source suspected, immune globulin is not indicated. Careful hygienic practices should be enforced. If an epidemiologic investigation indicates the source is from within one of these settings, immune globulin is indicated for contacts of index case.

MMWR(1999); 48(RR-12):1-37

Active Immunization with Hepatitis A Vaccine

Rationale for current immunization recommendations Despite the licensure of hepatitis A vaccine in 1995, hepatitis A remains one of the most frequently reported vaccine-preventable diseases in the United States. The approach of targeting high-risk individuals has been revised because of the limited projected impact on the overall incidence of hepatitis A in the United States.

Therefore, the national immunization strategy for hepatitis A prevention has shifted towards widespread routine immunization of children. Because of the high incidence of disease in children and their critical role in disease transmission, this strategy is the most effective way to reduce hepatitis A incidence nationwide over time. In addition, all persons identified at high risk for hepatitis A infection should be targeted for immunization.

√ National immunization strategy for hepatitis A is now primarily focused on the routine immunization of children.

√ Hepatitis A vaccine should be offered to children and adults in high-risk groups regardless of the rate of hepatitis A in the community.

CDC has recommended that widespread, routine immunization of children be implemented in states, counties, and communities that have sustained elevated rates of hepatitis A with incidence rates over 20 per 100,000 population. Average incidence rates from 1987-1997 demonstrate that 11 states are above this threshold, including Washington with an average annual hepatitis A incidence rate during that time period of 30 per 100,000.

In addition, regardless of the rate of disease in the community, immunization with hepatitis A vaccine is indicated for children at increased risk for hepatitis A infection and certain other risk groups:

- American Indian, Alaskan Native, and Pacific Islander children
- Migrant Hispanic children
- Males who have sex with other males
- Injecting drug users
- Individuals working with nonhuman primates

- Persons with clotting-factor disorders
- Persons with chronic liver disease

Washington State physicians and other health-care practitioners should be aware of the current (1999) recommendations for hepatitis A immunization made by the Advisory Committee on Immunization Practices (ACIP) of the CDC (*Table 4*).

Increased rates of hepatitis A have not been observed in food-service workers, sewage workers, health-care workers, or day-care attendees, and routine immunization of these populations is generally not warranted (*Table 5*).

√ Washington State physicians and other health-care providers should be aware of the current (1999) CDC recommendations for hepatitis A immunization.

Vaccine preparation
Hepatitis A vaccines contain
virus that has been grown in
human fibroblast cell cultures,
purified, and then formalin
inactivated and adsorbed to an
aluminum hydroxide adjuvant.
Currently, 2 of these vaccines
are licensed for use in persons
2 years of age and older in the
United States: HAVRIX® and
VAQTA®. HAVRIX® contains
2-phenoxyethanol as a preservative, while VAQTA® is formulated without a preservative.

Hepatitis A vaccines have demonstrated efficacy rates between 94-100% in controlled clinical trials. The vaccines are highly immunogenic in adults, adolescents, and children, with an estimated 100% of persons demonstrating antibody after the second dose; 80% of persons are protected at 2 weeks. and 95% are immune at 4 weeks. The vaccines stimulate the immune system to interrupt viral replication in the liver, leading to decreased fecal loads of virus and decreased transmissibility. Several reported hepatitis A outbreaks in small, well-defined communities have been effectively managed with immunization of a target population.

√ Hepatitis A vaccines have demonstrated efficacy rates of 94-100% in controlled clinical trials.

Hepatitis A vaccine is not licensed for use as post-exposure prophylaxis after an exposure to hepatitis A. Immunity should result 4 weeks after the first dose of vaccine: a second dose 6-12 months later is required for long-term protection. While no long-term data on vaccine efficacy are currently available, estimates based on kinetic models of antibody decline suggest that protection could last for 20 years or longer. Through surveillance of vaccines and population-based studies, eventual recommendations on booster immunizations may be made.

Table 4. Recommendations for routine hepatitis A vaccination in persons who are at risk for hepatitis A infection or serious outcomes

<u>Group</u>	<u>Comment</u>		
Children in communities with high rates of hepatitis A and periodic hepatitis A outbreaks	Recommended routinely for children 2 years of age and older in communities, counties, or states, with incidence rates of 20 cases per 100,000 ("high" risk). Consideration should be given for vaccination of children in areas with rates of 10-19 cases per 100,000 persons ("intermediate" risk).		
Men who have sex with men	Recommended for all MSM. Prevaccination testing not universally recommended for adolescents and young adults, although can be considered for older men.		
Users of illegal drugs	Recommended for both injecting and noninjecting drug users. Prevaccination testing not indicated for adolescents, although can be considered for older persons.		
Travelers to countries with intermediate or high rates of hepatitis A	An elevated risk exists even for those traveling to urban areas, those who stay in luxury hotels, and those who report that they have good hygiene and are careful about what they drink and eat. The first dose of vaccine should be given four weeks before travel. Persons traveling to a high-risk area less than four weeks after the initial dose of vaccine should receive an adjunct single dose of immune globulin (0.02 ml/kg) at a different injection site. Immune globulin alone is recommended for travelers less than 2 years of age. Prevaccination testing can be considered for older persons or persons in a high-risk group.		
	Travelers who are allergic to a vaccine component or who elect not to receive vaccine should receive a single dose of immune globulin (0.02 ml/kg), which provides effective protection against hepatitis A for up to 3 months. Travelers whose travel period exceeds 2 months should receive immune globulin at 0.06 ml/kg, which confers protection for up to 5 months; administration must be repeated if the travel period exceeds 5 months.		
Persons with chronic liver disease	Although persons with chronic liver disease do not have increased risk of hepatitis A infection, vaccination is recommended, since infections may be more severe. Vaccination is also recommended for chronic carriers of hepatitis B and/or C.		
Persons who have clotting- factor disorders	Prevaccination testing for hepatitis A titers is recommended. Susceptible persons who are administered clotting-factor concentrates (especially solvent-detergent-treated preparations) should be vaccinated.		
Persons who are pre- or post-liver transplant	Susceptible persons should be vaccinated.		
Persons who have an occupational risk of hepatitis A	Includes persons working with nonhuman primates and persons working with hepatitis A virus in research settings. No other occupational group has been shown to be at increased risk. **MMWR(1999); 48(RR-12):1-37*		

√ Four weeks after the first dose, 95% of vaccinated persons are protected. A second dose 6-12 months later is required for long-term protection.

Serologic testing for hepatitis A immunity prior to immunization may be done as a cost-control tool in subpopulations considered at high risk for previous infection. This group would include persons from countries with high rates of hepatitis A infection, elderly persons, certain MSM and illicit drug users, and persons with a clotting-factor disorder who may have received factor concentrates in the past. Due to the high immunogenicity of the vaccine, as well as the limitations of currently available commercial assays, it is not recommended to check antibody titers after immunization.

√ In persons considered at high risk for prior infection, serologic testing for hepatitis A antibodies may be done prior to immunization as a cost-control tool.

Table 5. Persons in whom hepatitis A vaccination is not routinely recommended

Group

- Children less than 2 years old
- Day-care attendees
- · Students and school employees
- Persons at institutions for developmental disabilities
- Food service workers

Comment: Consideration may be given to vaccination of employees who work in areas where community-wide outbreaks are occurring and where state and local health authorities or private employers determine that such vaccination is cost-effective.

Health-care workers

Comment: Routine infection control precautions when taking care of a patient with HAV infection are sufficient to prevent transmission to hospital staff.

Sewage workers

Comment: No work-related instances of hepatitis A transmission among sewage workers have been reported in the United States.

MMWR(1999); 48(RR-12): 1-37

Dosage schedules for hepatitis A immunization should adhere to the manufacturer's recommendations (Table 6). If the second dose of hepatitis A vaccine is delayed, it should be given as soon as possible; there is no need to repeat the first dose. Persons immunized with a schedule that mixed the two currently licensed vaccines have no decrease in the development of protective antibody and the vaccines are considered interchangeable. Hepatitis A vaccine can be given simultaneously with hepatitis B, diphtheria, polio (oral and inactivated), tetanus, oral typhoid, cholera, Japanese encephalitis, rabies, and yellow fever vaccines or with immune globulin, provided it is administered at a different injection site. The vaccine is given intramuscularly in the deltoid muscle.

The safety of hepatitis A vaccine in pregnancy has not been determined although the theoretical risk to the developing fetus is thought to be low. The risk associated with immunization should be weighed against the risk of hepatitis A in women who might be at high risk. Because the hepatitis A vaccine is inactivated, it is considered safe for immunocompromised persons. It is contraindicated in children less than 2 years of age and in persons with an allergy to a vaccine component.

No serious adverse events have been associated with either hepatitis A vaccine. In adults, the most common side effects are soreness at the injection site, headache, and malaise. In children, the most common side effects are soreness at the injection site, feeding problems, headache, and induration at the injection site. Rare occurrences of anaphylaxis, Guillain-Barrè syndrome, brachial plexus neuropathy, multiple sclerosis, and erythema multiforme have been reported, although there is no evidence for causality. Adverse events in both vaccines occur at a frequency similar to that of hepatitis B vaccine. If an adverse event is suspected to be associated with hepatitis A immunization, please contact the Vaccine Adverse Events Reporting System (VAERS) at 1-800-822-7967 or at http:// www.fda.gov/cber/vaers/ vaers.htm

√ No serious adverse events have been associated with the licensed hepatitis A vaccines.

Table 6. Recommended vaccination schedule for hepatitis A						
Vaccine	Age of Vaccinee (yrs)	Dose	Volume (ml)	Number of doses	Second Dose (mos)*	
HAVRIX® ¹	2-18	720 ELISA units	0.5	2	6-12	
	>18 years	1,440 ELISA units	1.0	2	6-12	
VAQTA®²	2-18	25 units	0.5	2	6-18	
	>18 years	50 units	1.0	2	6	

^{*}Months after initial dose

¹Hepatitis A vaccine, inactivated, SmithKline Beecham Biologicals

²Hepatitis A vaccine, inactivated, Merck & Co., Inc.

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Hepatitis A: Guide for Washington State Health Care Providers CME Credit Information and Post-Test Assessment

Course No. 483MED

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Washington School of Medicine and the University of Washington School of Public Health and Community Medicine. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this education activity for a maximum of 1.5 hours in category 1 towards the AMA Physician's Recognition Award. Each participant should claim only those hours of credit that he/

she actually spent in the educational activity To apply for category 1 credit, you must:

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- Enclose your credit card information or a check for \$30 made payable to the University of Washington
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Within three weeks following the receipt of this form, a transcript of your category 1 hours will be mailed to you. Credit hours for this monograph may be obtained from April 2001 through April 2004.

Evaluation Form We would appreciate your answ	vering the following questions	s in order to help us plan for	future activities of this type.		
 How would you rate: (please ✓) Value of the topic Relevance to your practice 	Excellent Good Fair Poor	3. Additional comments and/or suggested topics for future CME activities.			
c. Organization of monograph d. Publication length	·	L certify that I have sn	pent hour(s) to complete this		
e. Quality of information		education activity. (not to exceed 1.5 hours)			
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Registration Form Course No. 483MED Name (please print)	 Degree	Social Security No. (rec	quired for identification in our database)		
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Post Test: Course No. 483MED Hepatitis A

Please circle the correct answer.

1. Which of the following statements is NOT true concerning the clinical features of hepatitis A?

- A. The incubation period of hepatitis A averages 28 days.
- B. Adults are more likely to experience symptoms from hepatitis A virus (HAV) infection than are children.
- C. Symptomatic HAV infection in children is almost always accompanied by jaundice.
- D. Relapsing or prolonged hepatitis A infection can occur for up to 6 months.
- E. Hepatitis A infection cannot be differentiated from other types of viral hepatitis on the basis of clinical features alone.

2. What is the most frequently reported source of infection with HAV in Washington State?

- A. International travel
- B. Household or sexual contact with a person with hepatitis A
- C. Injection drug use
- D. Child day-care center attendance
- E. Blood transfusion

3. Which of the following groups is at increased risk of infection with HAV because of occupation?

- A. Employees of child day-care centers
- B. Food handlers
- C. Workers exposed to sewage
- D. Persons working with nonhuman primates
- E. All the above

4. Which of the following best describes the currently licensed hepatitis A vaccines?

- A. Live attenuated virus
- B. Inactivated virus
- C. Reassortant
- D. Toxoid
- E. Cloned DNA

5. Which of the following five conditions is a valid contraindication or precaution for the use of hepatitis A vaccine?

- A. Recent administration of antibody-containing blood product (e.g., whole blood or immune globulin)
- B. Infection with human immunodeficiency virus (HIV)
- C. Current administration of antibiotics.
- D. Severe allergy to a component of the vaccine
- E. All of the above

6. What is the most common adverse reaction following hepatitis A vaccine?

- A. Soreness at the injection site
- B. Fever

- C. An illness identical to hepatitis A
- D. Allergic reactions, such as angioedema
- E. Guillain-Barrè syndrome

7. Which of the following are among the groups recommended to receive routine hepatitis A vaccination?

- A. Injecting and noninjecting drug users
- B. Children ≥2 years of age who live in counties or communities where the average annual hepatitis A rate is 20 cases per 100,000 population or higher
- C. Men who have sex with men
- D. Persons with chronic liver disease
- E. All the above groups

8. Which of the following statements is considered a complication of hepatitis A?

- A. Cholestasis
- B. Prolonged and relapsing disease
- C. Fulminant hepatitis
- D. Acute liver failure
- E. All of the above

9. Which of the following is NOT true regarding hepatitis A?

- A. Hepatitis A rates in Washington State are nearly twice the national average
- Rates of hepatitis A and groups at risk for infection may vary considerably from year to year and between communities
- C. Since infected children are frequently asymptomatic, they are an important and frequently unrecognized source of infection
- D. Most hepatitis A cases have easily recognized risk factors
- E. Hepatitis A is transmitted by the fecal-oral route

10. Which of the following statements is NOT true?

- A. Two doses of hepatitis A vaccine given 6-12 months apart are required for full protection
- B. In persons exposed to a case of hepatitis A, hepatitis A vaccine may be given at the same time as immune globulin (IGIM) to confer long-term protection.
- C. Health-care providers in Washington State are required to report confirmed and suspected cases of hepatitis A to their local health departments immediately.
- D. The duration of protection against hepatitis A infection from standard doses of immune globulin (IGIM) is several months.
- E. Antibody titers should be checked routinely after hepatitis A immunization.